

**REMARKS****Rejection of Claim 42 Under 35 U.S.C. § 112, First Paragraph**

Claim 42 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner alleges that there is no original disclosure of the cause of the glucose intolerance recited in claim 42.

Applicants respectfully traverse the rejection. Although the Examiner states that he was unable to locate a copy of the article cited at page 51, line 6 of the specification, it is noted that a copy of this article and an English translation thereof were provided as Exhibit A with the Reply mailed April 20, 2004. For the Examiner's convenience, an additional copy of the reference and translation are attached hereto as Exhibit A. Applicants further note that the correct citation is *Z. Gastroenterol.* (1997) 35: 655-8, not *Gastroenterol.*; the correct citation is provided in the specification.

Claim 42 is directed to a method of modifying glucose metabolism of a glucose intolerant animal, where the glucose intolerance is a result of a deletion or disruption of the gene encoding for a glucagon type peptide 1 (GLP-1) receptor. Although the specification provides a discussion of the effect of GLP-1 deletion in mice, the cited article (Exhibit A) makes it clear that the effects of GLP-1 on animals in general was well-known as of the effective filing date of the instant application. Page 4, lines 30-31 of the translation states: "GLP-1 and its pronounced stimulation of insulin secretion have been known for approximately ten years." As shown in Exhibits B and C (attached hereto), both of which were publicly available as of the effective filing date, the effects of GLP-1 on glucose intolerance were also recognized in rats and humans. Based upon the well-known effects of GLP-1 on glucose intolerance in several species, in combination with the disclosure that knockout of the GLP-1 receptor in mice causes glucose intolerance, sufficient description is present to support a limitation to deletion or disruption of the GLP-1 receptor causing glucose intolerance generally in animals. Moreover, according to the translation in Exhibit A, page 4, lines 20-29, an antagonist of the GLP-1 receptor was

known, which suggests that any disruption of the GLP-1 receptor (including those caused by genetic disruptions) will affect glucose intolerance. Reconsideration and withdrawal of the rejection are respectfully requested.

Provisional Rejection of Claims 38-42 and 46-68 Under Obviousness-Type Double Patenting

Claims 38-42 and 46-68 are provisionally rejected under obviousness-type double patenting over U.S. Application Nos. 09/601,432, 10/190,267 and 10/794,316. Applicants request that the Examiner hold these provisional rejections in abeyance until allowable subject matter is identified in the instant application. According to MPEP 804, “[t]he ‘provisional’ double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that ‘provisional’ double patenting rejection is the only rejection remaining in one of the applications. If the ‘provisional’ double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the ‘provisional’ double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.”

Rejection of Claims 38-40, 46-53 and 68 Under 35 U.S.C. § 102(e)

Claims 38-40, 46-53 and 68 are rejected under 35 U.S.C. § 102(e) as being anticipated by Villhauer (US 6,011,155).

In order for Villhauer to anticipate claims 38-40, 46-53 and 68, it must teach, in an enabling manner, the method of modifying glucose metabolism of a glucose intolerant animal with a single daily oral dosage of a DPIV inhibitor. Applicants reiterate that Villhauer does not provide an enabling disclosure for modifying glucose metabolism of a glucose intolerant animal. As proof of non-enablement, the only *in vivo* experiment Villhauer provides is the administration of compounds to male Sprague-Dawley rats and measurement of early insulin response (see col. 9, line 66 to col. 10, line 28). There is no disclosure that these rats are glucose intolerant or that the experimental model is representative of results that would be obtained from glucose intolerant rats. In contrast, Applicants show in Figure 4 that a GLP-1 receptor -/- transgenic mice has high blood glucose, which is ameliorated by administration of a compound of the present invention. The animal models used by Applicants are truly glucose intolerant. As such,

Applicants assert that Villhauer does not teach all the elements of the instant claims, and therefore fails to anticipate the claims. Reconsideration and withdrawal of the rejection are requested.

Rejection of Claims 38-40, 46-53 and 68 Under 35 U.S.C. § 103(a)

Claims 38-40, 46-53 and 68 are rejected under 35 U.S.C. § 103(a), as being obvious over DE 196 16 486 (hereinafter “the ‘486 Patent”). The Examiner alleges that the Declarations under 37 CFR 1.131 (hereinafter “the Declarations”) are not sufficient to antedate the ‘486 Patent because the declarations do not allege that the acts relied upon to establish the date were carried out in this country, a NAFTA country or a WTO member country.

Applicants maintain that the ‘486 Patent is not available as prior art, and that the Declarations are sufficient to antedate the ‘486 Patent. In particular, Applicants maintain that the Declarations include an adequate statement that the acts relied upon to establish a date were carried out in this country, a NAFTA country or a WTO member country. Section 4 of the Plaut Declaration states that Plaut sent a batch of Pro(boro)Pro to Drucker, meaning that the Pro(boro)Pro was sent to Toronto, Canada, as evidenced by Exhibit C to the Plaut Declaration. Also, Section 4 of the Drucker Declaration states that the Pro(boro)Pro sample was received from Plaut, and that this sample was used to carry out the experiments on GLP-1 +/- and -/- mice. From these statements and Exhibit C, it is clear that the following experimental work took place in Canada, a NAFTA country.

According to Section 4 of the Drucker Declaration, oral glucose tolerance test (OGTT) experiments began within 4 months of having sent the e-mail of Exhibit A, which was sent prior to June 1997. Thus, the OGTT experiments commenced prior to October 1997. These experiments represent an actual reduction to practice of the present invention. Because the ‘486 Patent did not publish until October 30, 1997, the acts described in the Declarations antedate the ‘486 Patent. There is no need to establish diligence following conception of the invention in order to antedate the ‘486 Patent.

Thus, Applicants maintain that the Declarations are sufficient to antedate the ‘486 Patent, such that it is not available as prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above remarks and amendments, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee is due with this response, aside from the fee associated with the Petition for Extension of Time. However, if an additional fee is due, please charge our Deposit Account No. 18-1945, from which the undersigned is authorized to draw, under Order No. TUU-P01-006.

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Respectfully submitted,

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